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The relationship between the indicators of the retina condition and other target organ changes in uncomplicated essential hypertension

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Abstract

Background. Changes in retinal microcirculation are considered a subtle indicator of the other target organ damage in hypertension and might have prognostic value. **Objective.** To establish the relationship between diameters of retinal arterioles and venules, foveal avascular zone (FAZ) area, subfoveal choroid thickness with parameters of left heart and kidneys in middle-aged patients with essential hypertension (EH) stage I–II. **Design and methods.** A total of 115 people (86 males, 29 females) aged 45–59 years were examined and divided into 2 groups. The main group consisted of 70 patients with EH stage I or II. The control group comprised 45 normotensive practically healthy individuals. Patients with diabetes mellitus, impaired liver function, clinically significant ophthalmic pathology were not included. The following data were analyzed: anamnesis including smoking status; routine blood hemodynamic and biochemical parameters, serum procollagen III N-terminal propeptide (PIIINP); albumin-creatinine ratio in a single morning portion of urine, diurnal albuminuria; parameters of 24-h ambulatory blood pressure monitoring; quantitative electrocardiography (ECG) markers of left ventricular hypertrophy; transthoracic echocardiography; fundus state. Based on the scanning laser ophthalmoscopy, the central retinal arterial (CRAE) and venous (CRVE) equivalents, arteriovenous ratio (AVR) were calculated. Using the method of optical coherence tomography angiography, we determined the FAZ area and subfoveal choroid thickness. Statistical data were processed using the StatSoft Statistica 10. **Results.** Compared with normotensive individuals, patients with hypertension were characterized by lower values of CRAE ($p = 0.009$), larger FAZ area ($p = 0.019$), and comparable values of CRVE, AVR, subfoveal choroid thickness ($p > 0.05$ for each indicator). Correlation analysis showed that in hypertensive AVR correlated with low-density lipoprotein cholesterol level ($r = –0.3$; $p < 0.05$); FAZ area with female gender ($r = 0.42$; $p < 0.05$); FAZ area with PIIINP level ($r = 0.3$; $p < 0.05$); FAZ area with diurnal albuminuria ($r = 0.37$; $p < 0.05$); CRVE with R wave amplitude in aVL lead of ECG ($r = 0.31$; $p < 0.05$); CRAE with left atrial volume index ($r = –0.3$; $p < 0.05$); subfoveal choroid thickness with age ($r = –0.3$; $p = 0.01$). **Conclusions.** Middle-aged patients with uncomplicated EH are characterized by the lower CRVE values and larger FAZ area compared to normotensive individuals. In EH stage I–II,

retinal microcirculation parameters are associated with indicators reflecting the other target organ damage, in particular, the left atrial volume index, R wave amplitude in aVL lead of the standard ECG, diurnal albuminuria, and serum PIIINP concentration.

Key words: hypertension, average age, target organ, retina, myocardium, kidney, correlation

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Взаимосвязь показателей состояния сетчатки с другими органными изменениями при неосложненной гипертонической болезни

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Резюме

Актуальность. Изменения ретинальной микроциркуляции считаются тонким индикатором состояния других органов-мишеней артериальной гипертензии (АГ) и могут иметь прогностическое значение. **Цель исследования** — установить взаимосвязь диаметров ретинальных артериол и венул, площади фовеальной аваскулярной зоны (ФАЗ), субфовеальной толщины хориоидеи (СТХ) с показателями, характеризующими состояние левых отделов сердца и почек у пациентов среднего возраста с гипертонической болезнью (ГБ) I–II стадии. **Материалы и методы.** Обследовали 115 человек (86 мужчин и 29 женщин) в возрасте от 45 до 59 лет. Основную группу составили 70 пациентов с гипертонической болезнью (ГБ) I или II стадии. Группу контроля сформировали из 45 нормотензивных практически здоровых лиц. В исследование не включали пациентов с сахарным диабетом, нарушениями функции печени, клинически значимой офтальмологической патологией. Проводили анализ следующих данных: анамнестических особенностей с оценкой статуса курения; значений рутинных гемодинамических и биохимических показателей крови, N-терминального пропептида III проколлагена (PIIINP) крови; альбумин-креатининового соотношения в разовой утренней порции мочи, суточной альбуминурии; параметров 24-часового амбулаторного мониторирования артериального давления; количественных электрокардиографических (ЭКГ) маркеров гипертрофии левого желудочка; трансторакальной эхокардиографии; состояния глазного дна. На основе метода сканирующей лазерной офтальмоскопии рассчитывали центральный артериальный (ЦАЭС) и венозный (ЦВЭС) эквиваленты сетчатки, артериовенозное соотношение (АВС). Методом оптической когерентной томографии определяли площадь ФАЗ и СТХ. Статистическую обработку данных осу-

ществляли с применением пакета прикладных программ StatSoft Statistica 10. **Результаты.** Пациенты с АГ по сравнению с нормотензивными лицами характеризовались: меньшими значениями ЦАЭС ($p = 0,009$), большей площадью ФАЗ ($p = 0,019$), сопоставимыми величинами ЦВЭС, АВС, СТХ ($p > 0,05$ для каждого показателя). В результате выполненного корреляционного анализа в группе пациентов с АГ были выявлены взаимосвязи: АВС и уровня холестерина липопротеинов низкой плотности ($r = –0,3$; $p < 0,05$); площади ФАЗ и принадлежности к женскому полу ($r = 0,42$; $p < 0,05$); площади ФАЗ и содержания в крови PIIINP ($r = 0,3$; $p < 0,05$); площади ФАЗ и суточной альбуминурии ($r = 0,37$; $p < 0,05$); ЦЭВС и амплитуды зубца R в отведении aVL на ЭКГ ($r = 0,31$; $p < 0,05$); ЦАЭС и индекса объема левого предсердия (ЛП) ($r = –0,3$; $p < 0,05$); СТХ и возраста ($r = –0,3$; $p = 0,01$). **Заключение.** Пациенты среднего возраста с неосложненной эссенциальной АГ характеризуются меньшими значениями ЦАЭС и большей площадью ФАЗ по сравнению с нормотензивными лицами. При ГБ I–II стадии параметры ретинальной микроциркуляции ассоциированы с показателями, отражающими состояние других органов-мишеней АГ — индексом объема ЛП, амплитудой зубца R в отведении aVL стандартной ЭКГ, суточной альбуминурией и сывороточной концентрацией PIIINP.

Ключевые слова: артериальная гипертензия, средний возраст, орган-мишень, сетчатка, миокард, почка, корреляция

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Foreword

Essential hypertension (EH) is often associated with asymptomatic lesions of target organs. Purposeful screening is able to detect electrocardiographic and/or ultrasonic signs of left ventricular hypertrophy (LVH), microalbuminuria, thickening of the intima-media complex, acceleration of the arterial pulse wave, ophthalmoscopic manifestations of hypertensive retinopathy [1, 2]. The latter, as a rule, is present in combination with changes in other target organs. The initial stages (the first and second stages according to the Keith-Wagener-Barker classification) of microvascular fundus changes (generalized or focal narrowing of arterioles, decrease in arteriovenous ratio, arteriovenous crossing) are considered as a relatively weak indicator of targeted vascular and other organ changes in patients with systemic hypertension [3, 4]. At the same time, hypertensive retinopathy of the third and fourth stages serves as a significant predictor of cardiovascular events, independent of existing changes in other target organs caused by high blood pressure (BP) [5, 6].

In real practice high stages of hypertensive retinopathy are quite rare and can reflect not only the malignant course of hypertension, but also indicate its secondary nature [7]. In recent years, the attention of specialists was focused on the study of the pathogenic and prognostic role of indicators characterizing the foveal avascular zone (FAZ), as well as the choroid, obtained using optical coherent tomographic angiography in hypertensive subpopulations [8–10, 11–13]. The aim of the study was to establish the relationship between the diameters of retinal arterioles and venules, the area of the FAZ, subfoveal choroid thickness with indicators characterizing the condition of the cardiac left parts and kidneys in middle-aged patients with uncomplicated EH.

Design and methods

115 people aged from 45 to 59 years were selected to participate in the study. The main group consisted of 70 patients (56 males and 14 females, average age 49.7 ± 4.8 years), suffering from stage 1 or 2 EH and having a 1–3 degree increase in office BP. The stage and degree of hypertension were established according to the current Guidelines of the European Society of Cardiology and European Society of Hypertension (ESC/ESH, 2018) [14]. We didn't include patients with diabetes mellitus, individuals with ischemic heart disease, impaired liver function, chronic kidney disease of the 4th and 5th stages, as well as ophthalmic pathology (history of penetrating eye injuries, diseases of the eyelids, sclera, cornea, iris, vitreous body, cataract, glaucoma, high myopia, dystrophy and retinal detachment, hypertensive retinopathy of stages the 3rd and 4th according to Keith-Wagener-Barker classification). The control group consisted of 45 normotensive individuals (30 males and 15 females, average age 49.3 ± 4.7 years) without cardiovascular and other clinically significant internal pathologies. All participants of the study signed a consent form voluntarily.

Most patients who were included in the main group regularly took antihypertensive drugs: 67 % — angiotensin-converting enzyme inhibitors, 16 % — angiotensin receptor blockers, 27 % — dihydropyridine calcium antagonists, 31 % — thiazide or thiazide-like diuretics, 4 % — beta-blockers. In addition, in the interests of cardiovascular diseases primary prevention, 10 % and 8 % of hypertensive patients regularly took statins and aspirin respectively. The normotensive participants didn't receive any cardiovascular therapy.

In individuals of the main and control groups, the following data were analyzed: anamnestic features with an assessment of a smoking status; BP and heart rate obtained at rest during office measurement; blood biochemical parameters, including the level of total cholesterol, triglycerides, high and low density lipoprotein cholesterol, glucose, creatinine, urea, N-terminal procollagen III propeptide (PIIINP); urine analysis indicators, including albumin-creatinine ratio in a single morning portion, 24-h albuminuria; parameters of ambulatory 24-h BP monitoring; quantitative ECG markers of LVH; transthoracic echocardiography; retina condition.

Images of retinal vessels were obtained with the help of F10 scanning laser ophthalmoscope (Naidec Co., LTD, Japan) in the IR (infrared light) mode with centering on the optic disc. The diameters (μm) of the four largest branches of the central artery and the four largest branches of the central retinal vein were measured at a distance of 0.5–1 diameter of the disk from its edge. When assessing caliberometric vascular parameters in order to standardize the data and the possibility of objective comparison among the study participants, specialized equivalents were used — the central retinal arterial (CRAE, μm) and venous (CRVE, μm) equivalents, which were calculated using the modified Parr-Hubbard-Knudtson formula [15]. The arteriovenous ratio (AVR) was obtained by dividing the value of the central retinal arterial equivalent by the value of the central retinal venous equivalent. The area of the FAZ (mm^2) and the subfoveal choroid thickness (SCT, μm) were measured using an RTVue-100 XR Avanti optical coherent tomograph (Optovue, USA). During optical coherence tomography angiography (OCTA), two volumetric scans were performed in orthogonal directions (horizontal and vertical). Figure 1 shows the technique for measuring the diameters of arterioles and venules of the fundus, which are necessary for calculating CRAE and CRVE.

Using the Angio Retina 3 mm protocol (2 series of 200 B scans, each of which was obtained on the basis of 1024 A scans), the FAZ area was determined at the level of the superficial retinal capillary plexus. In accordance with the Cross-line protocol (1024 A-scans), a horizontal scan of the subfoveal choroid thickness (μm) was performed in the central part of the fovea, while measurements were carried out manually in the tomograph software. When implementing the OCTA methodology and interpreting the obtained data, the results described by experts in this field were taken into account [16–18]. Figure 2 shows the technique for measuring the area of the FAZ and subfoveal choroid thickness.

Statistical data processing was carried out using StatSoft Statistica 10 application software package. MS Excel from MS Office 2013 was used for preparing the research matrix. We used parametric statistics (comparison of means using Student's t-test, determination of the correlation coefficient (r) to assess the strength, direction and significance of the relationship between the attributes) to compare the quantitative indicators obeying the law of normal distribution.

Figure 1. Technique for measuring the diameters of arterioles (fragment A) and venules (fragment B) of the fundus required for calculating the central retinal arterial equivalents and the central retinal venous equivalents

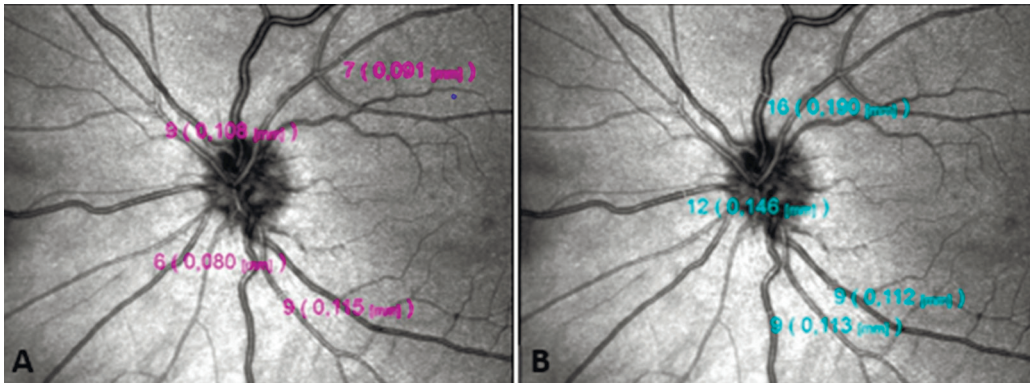
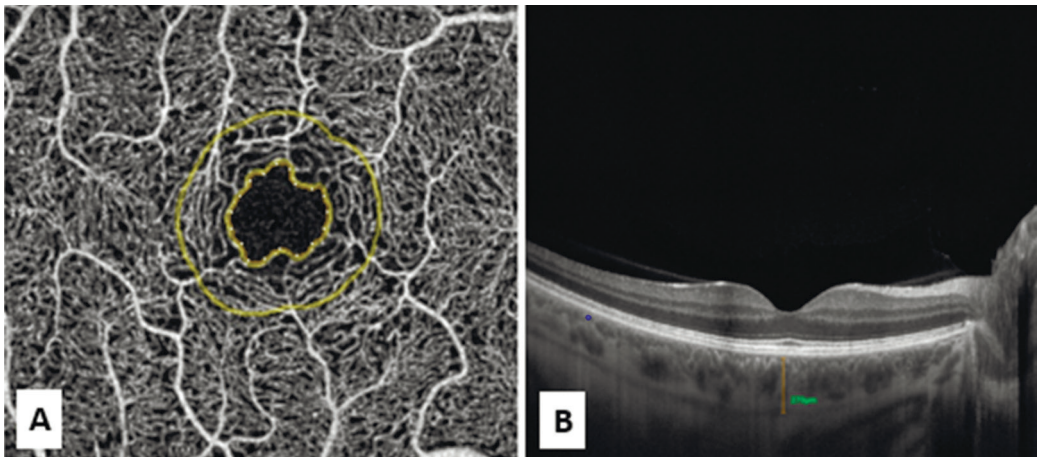


Figure 2. Technique for measuring the foveal avascular zone area (fragment A) and subfoveal choroid thickness (fragment B)



Note: the inner contour at the level of the superficial capillary plexus corresponds to the boundaries of the foveal avascular zone (fragment A), the segment reflects the subfoveal choroid thickness (fragment B).

A non-parametric statistics module was used (non-parametric U-test Mann-Whitney, Spearman's rank correlation coefficient r) to study the relationships between qualitative indicators and indicators that do not obey the law of normal distribution. $P < 0.05$ was taken as a critical level of significance. When describing intergroup differences, data were presented as mean (M) ± standard deviation (Std. D.).

Results

Table 1 shows the baseline characteristics of the study participants. Individuals of the main and control groups did not differ in age ($p > 0.05$), office heart rate ($p > 0.05$). As compared to normotensive subjects, patients with EH were characterized by significantly higher values of the waist circumference ($p < 0.001$), office systolic ($p < 0.001$) and diastolic ($p < 0.001$) BP.

In patients with hypertension, the plasma glucose and low density lipoprotein cholesterol (LDL cholesterol) in blood serum, the estimated glomerular filtration rate (GFR) did not differ from those in normotensive individuals ($p > 0.05$). The 24-h albuminuria and the level of PIIINP in the blood of individuals of the main group significantly exceeded those subjects from the control group ($p = 0.001$; $p < 0.001$, respectively). The albumin-creatinine ratio in a single portion of morning urine in both examined groups did not significantly differ ($p > 0.05$).

The study participants, regardless of the level of BP, had normal values of Sokolow-Lyon index, the amplitude of R wave in the lead aVL, the Cornell voltage product. At the same time, each of the considered ECG parameters in patients with hypertension significantly exceeded that of normotensive study participants ($p = 0.035$; $p = 0.004$; $p < 0.001$, respectively).

As compared to normotensive individuals, patients with hypertension had higher left ventricular myocardial mass (LVMM) and left atrial volume ($p < 0.001$; $p = 0.059$, respectively) indexed by body surface area (LVMMI and LAVI respectively). The contractility and diastolic function of the left ventricle (LV) in the examined individuals were not impaired. The ejection fraction of the LV, the averaged peak rate of early diastolic displacement of the lateral and septal parts of the mitral valve ring (e'), as well as the calculated E/e', did not differ significantly between hypertensive and normotensive subjects ($p > 0.05$ for each indicator).

Table 2 shows the comparative characteristics of retinal parameters in the examined individuals. CRAE was significantly less in individuals with hypertension compared with the control ($p = 0.009$). CRVE in hypertensive patients was higher than that of normotensive subjects ($p > 0.05$). The calculated parameter, AVR, in patients of the main group was not considerably inferior to that in the control group ($p > 0.05$).

It is noteworthy that the absolute values of CRAE in the hypertensive and normotensive groups were close, but significantly different, which may be due to low intragroup variability, regardless of their belonging to the BP range. Compared with the control group, patients with hypertension were characterized by a significantly larger FAZ area ($p = 0.019$) and a comparable SCT ($p > 0.05$).

As a result of the correlation analysis in the group of patients of the main group, statistically significant

Table 1

BASELINE CHARACTERISTICS OF EXAMINED INDIVIDUALS (M ± S.D.)

Parameters	Patients with EH (n = 70)	Normotensive individuals (n = 45)	p-value
Age, years	49.7 ± 4.8	49.3 ± 4.7	0.6
Waist circumference, cm	99.3 ± 16.5	87.6 ± 16.1	< 0.001
Office systolic BP, mmHg	142.5 ± 14	123.3 ± 10.9	< 0.001
Office diastolic BP, mmHg	86 ± 16.8	78 ± 11.1	< 0.001
Office heart rate, per min	72 ± 8.9	70.4 ± 9.6	0.365
Plasma glucose, mmol/l	5.4 ± 1.45	5.3 ± 1.24	0.236
LDL Cholesterol, mmol/l	3 ± 1.1	3.1 ± 1	0.64
GFR, ml/min	80.1 ± 12.5	76.6 ± 13	0.22
Albumin Creatinine ratio, mg/g	2.6 ± 1.5	2.2 ± 1.4	0.135
24-h albuminuria, g	0.05 ± 0.08	0.01 ± 0.02	0.001
PIIINP, ng/ml	1.61 ± 0.76	1.52 ± 0.55	< 0.001
Sokolow-Lyon index, mm	22.5 ± 6.2	20.1 ± 5.4	0.035
RaVL, mm	5.6 ± 2.9	4.1 ± 2.5	0.004
Cornell voltage product, mm•ms	1478 ± 545	1049 ± 402	< 0.001
LVMMI, g/m^2	110 ± 35	86.8 ± 20.7	< 0.001
LAVI, ml/m^2	26.2 ± 8.6	23.2 ± 8.5	0.059
LV EF, %	66.5 ± 8.5	69.6 ± 9.6	0.077
e', m/s	0.14 ± 0.1	0.13 ± 0.03	0.389
E/e'	5.6 ± 2	5.9 ± 1.5	0.199

Note: EH — essential hypertension; BP — blood pressure; LDL — low density lipoprotein; PIIINP — N-terminal procollagen III propeptide; GFR — glomerular filtration rate; LVMMI — left ventricular myocardial mass index; LAVI — left atrium volume index; LV EF — left ventricular ejection fraction; e' — the average peak velocity of the early diastolic displacement of the lateral and septal parts of the mitral valve ring; E/e' — the ratio of the maximum flow rate of the early diastolic filling of the left ventricle to the average peak velocity of the early diastolic displacement of the lateral and septal parts of the mitral valve ring.

Table 2

CHARACTERISTIC OF RETINAL PARAMETERS IN THE EXAMINED INDIVIDUALS (M ± S.D.)

Parameters	Patients with EH (n = 70)	Normotensive individuals (n = 45)	p-value
CRAE, μm	138 ± 12.4	143 ± 11.5	0.009
CRVE, μm	223 ± 22.7	218 ± 20.5	0.878
AVR	0.61 ± 0.07	0.65 ± 0.09	0.1
FAZ area, mm^2	0.32 ± 0.10	0.26 ± 0.08	0.019
SCT, μm	313 ± 85.8	302 ± 87.8	0.526

Note: CRAE — central retinal arterial equivalent; CRVE — central retinal venous equivalent; AVR — arteriovenous ratio; FAZ — foveal avascular zone; SCT — subfoveal choroid thickness.

associations of the studied ophthalmic indicators with separate laboratory and instrumental parameters characterizing the cardiovascular risk and prognosis were established. Most correlations were weak. Table 3 demonstrates the AVR obtained by scanning the fundus had a negative association with the level of LDL cholesterol (r = –0.3), the FAZ area was positively correlated with female gender (r = 0.42), the level of PIIINP (r = 0.3) and 24-h albuminuria (r = 0.37). CRVE was associated with the amplitude of the R wave in the lead aVL (r = 0.31), and CRAE negatively correlated with LAVI (r = –0.3). The SCT turned out to be inversely related to age (r = –0.3).

Discussion

It was established that the patients with hypertension examined by us were characterized by a significantly smaller calculated diameter of arterioles and a

Table 3

ЗНАЧИМЫЕ СВЯЗИ ИЗУЧЕННЫХ РЕТИНАЛЬНЫХ ПОКАЗАТЕЛЕЙ В ГРУППЕ ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

Parameter № 1	Parameter № 2	Correlation coefficient r	p-value
CRVE, μm	RaVL, mm	0.31	< 0.05
CRAE, μm	LAVI, ml/m^2	–0.3	< 0.05
AVR	LDL Cholesterol, mmol/l	–0.3	< 0.05
FAZ area, mm^2	PIIINP, ng/ml	0.3	< 0.05
FAZ area, mm^2	24-h albuminuria, g	0.37	< 0.05
FAZ area, mm^2	Female gender	0.42	< 0.05
SCT, μm	Age, years	–0.3	0.01

Note: CRAE — central retinal arterial equivalent; CRVE — central retinal venous equivalent; AVR — arteriovenous ratio; FAZ — foveal avascular zone; SCT — subfoveal choroid thickness; LDL — low density lipoprotein; PIIINP — N-terminal procollagen III propeptide; LAVI — left atrium volume index.

comparable calculated diameter of retinal venules as compared with normotensive individuals. The calculation formula for CRAE and CREC was tested by R. Heitmar et all (2015) in a healthy subpopulation. According to the authors, the interval of CRAE values obtained in the framework of this study ranged from 145 to 151 μm, and CRVE values ranged from 205 to 227 μm. The AVR among the individuals examined in the main and control groups did not show itself in the aspect of detecting significant differences due to the influence of the factor of hypertension.

The relationship of the retinal vessels calibers with factors of cardiovascular risk is generally known. The inverse association of the AVR with LDL cholesterol serum level, revealed in our study, to some extent corresponds to the results established in much larger research projects, such as ARIC, MESA, Tromsø Eye Study [3, 19, 20]. The authors of these studies stated that venous expansion plays a greater role in this association than constriction of arterioles. It is emphasized that dilatation of retinal venules serves not only as a marker of the burden of exposure to various risk factors (systemic hypertension, smoking, dyslipidemia), but also of ongoing systemic low-intensity inflammation and endothelial dysfunction [21].

It is proved that microvascular dysfunction is one of the key elements of hypertension pathogenesis. At the same time, narrowing of the arterioles and expansion of the fundus venules carries a different informative load in terms of prognosis, therefore, their differentiated assessment may be more important than determining the AVR [19]. In addition, the results of some studies led to the conclusion that, along with the retinal arterioles narrowing, the expansion of the venules, regardless of other factors, correlates with the probability of revealing hypertension [19].

There is an idea of venous dilatation as a marker of retinal ischemia and secondary hypoperfusion due to microvascular rarefication [22]. It was established that dilatation of retinal venules is interconnected with systemic low-intensity inflammation, laboratory and instrumental markers of atherosclerosis, and other metabolic abnormalities [21]. Interpreting our own results in terms of the association of elevated BP with fundus vascular changes, the publication of J. Ding et al. (2014), in which the authors evaluated the relationship between the caliber of retinal vessels (considered as a marker of systemic microvascular dysfunction) and the likelihood of arterial hypertension based on a meta-analysis of individual data obtained from 10.229 subjects without hypertension, diabetes mellitus, and cardiovascular diseases. As a result of follow-up for 2.9–10 years, hypertension was recorded in 2599 study participants. A decrease in CRAE for every 20 μm, as well as an increase in CRVE for every 20 μm, were accompanied by an increase in the risk of hypertension debut by 29 % and 14 % respectively. The authors of the meta-analysis concluded that narrowing of the retinal arterioles and expansion of the retinal venules, independently of other factors, are associated with the onset of hypertension, thereby confirming the pathogenic role of microcirculatory disorders in the formation of hypertension [23].

We found weak, but significant, correlations of CRVE with RaVL, as well as CRAE with LAVI. To some extent, these data confirm performances of other researchers who established in cross-sectional and prospective studies a significantly higher prob-

ability of quantitative signs of LVH on the ECG, and also ultrasonic signs of an increase in the cardiac left chambers in case of detection of ophthalmoscopic retinal microvascular changes [24, 25].

At the same time, it was noted that ECG criteria of LVH were observed only in 10% of patients with the 1st or 2nd stage of hypertensive retinopathy [25]. Patients with the presence of quantitative ECG criteria of myocardial hypertrophy did not actually participate in our study. Therefore, the absolute values of Sokolow-Lyon index, RaVL, Cornell voltage product, and the absolute values of the calculated retinal arterioles and venules diameters were taken into account in the correlation analysis.

The relationship between the CRAE and the LAVI, revealed in the current work, indirectly confirms the information given in some publications [25, 26], which testify to the correspondence of retinopathy severity to the degree of LA dilatation in hypertension. An association of changes in the retinal vessels diameters with structurally functional kidneys and aorta disorders is reported. So, in a small pilot project Q.X. Huang et all (2013) demonstrated a significant negative correlation between CRAE and the albumin-creatinine ratio in a single urinal portion in patients with hypertension [27].

In a study by P. Kangwagye et all (2018), performed in a rather large cohort of hypertensive individuals, there was found a significant association of arteriolar constriction and venular dilation (evaluated by traditional ophthalmoscopy) with 24-h albuminuria and proteinuria [28]. M. Meyer et all (2020) stated that in elderly patients, an increase in CRVE has a closer correlation with carotid-femoral pulse wave velocity than a decrease in CRAE [29]. Microvascular morphological and physiological properties of the retina can be considered as a thin prospective indicator in assessing the damage to target organs (heart, brain, kidneys) in hypertensive patients [30, 31].

It is assumed that the reduction in the density of the superficial and deep capillary plexuses is due to the narrowing of the retinal arteriolar microvascular bed, resulting not only from prolonged exposure to systemic arterial hypertension, but also from fluctuations in BP over a short period of time, as well as the effect of BP at the time of fundus examination [32]. An increase in the resistance of the retinal microvasculature contributes to a decrease in the blood flow volume and capillary density. In a recently published study by H.B. Lim et all (2019) it was demonstrated that in patients with a history of hypertension for more than five years, capillary density in the foveal region is significantly lower than that in patients who have a shorter history of increased BP [33]. FAZ area boundaries are more clearly defined at the level of superficial (rather than deep) capillary plexus [8]. At the same time, the authors report significant variability in the FAZ area established in groups of healthy individuals by various research teams. W.A. Samara et all (2015) analyzed eleven available original publications, stating that among healthy individuals, the superficial FAZ area varied in the range of 0.167–0.430 mm² [8]. The data on the change in the FAZ area in hypertension without concomitant diabetes mellitus are relatively few. So, in a small pilot study (n = 45) S. Donati et al. (2019) showed that hypertensive patients who received continuous antihypertensive therapy had a significantly larger FAZ area evaluated at the level of deep capillary plexus than patients with newly diagnosed hypertension and healthy subjects (0.39 ± 0.1 mm²; 0.36 ± 0.07 mm²; 0.34 ± 0.09 mm², respectively) [11]. At the level of the superficial capillary plexus, the researchers did not establish significant differences in the FAZ area in the examined individuals without hypertension, patients with the first detected hypertension and in patients receiving antihypertensive therapy, although they noted a tendency to expand the boundaries of FAZ area in hypertension [11].

D. Hua et all (2019), having examined a cohort of people aged 60 to 70 years, also found an increase in the FAZ area as arterial hypertension occurs and progresses (in healthy subjects the FAZ was 0.300 ± 0.09 mm², in patients with a history of hypertension from 5 to 10 years — 0.372 ± 0.11 mm², in patients with a history of hypertension over 10 years — 0.388 ± 0.18 mm²) [34]. Own data indicate a significant expansion (within the reference range of values) of the FAZ area in middle-aged normoglycemic hypertensive individuals compared to normoglycemic normotensive subjects. Intergender differences in relation to the size of the FAZ area in hypertensive population require further investigations, since the relevant information at the current stage in healthy and sick individuals is scattered. At the same time, a number of authors report a tendency towards a predominance of the FAZ area values in female subpopulations [8–10]. We obtained a significant correlation between the FAZ area and the female gender among hypertensive patients confirms the existing ideas in this aspect. The age-related dynamics of the FAZ area in healthy and hypertensive individuals continues to be actively studied. So, using the method of OCTA, W.A. Samara et all (2015) were not identified, but N.A. Iafe et all (2016) and

A. Shahlaee et all (2016) found a significant correlation of the FAZ area at the level of the superficial retinal capillary plexus with age.

The relationship between the FAZ area and renal function is studied in more detail in type 1 and type 2 diabetes mellitus patients [8, 35], to a lesser extent is studied in healthy individuals [35]. In particular, R. Sato et al. (2019) showed that in a healthy population, changes in the FAZ area and GFR are multidirectional with age increasing, and a negative correlation of these indicators does not have statistical significance [36]. In our work, a significant positive association of the FAZ area and 24-h albuminuria in uncomplicated hypertension was established, confirming the simultaneity of changes in the corresponding target organs. It seems logical that we obtained a significant correlation of the FAZ area and the serum level of the N-terminal propeptide III of procollagen. PIIINP is considered as biomarker of matrix remodeling, reflecting the rate of production of fibrous tissue in the myocardium, kidneys in cardiovascular diseases, heart failure, diabetes mellitus, systemic immune inflammation [37–40].

At the same time, we did not find a significant relationship between the serum content of PIIINP and CRAE, CRVE. In the Cardiovascular Health Study, researches also did not establish an association of blood PIIINP level and retinal arteriolar and venular equivalents, which, according to the authors, is not surprising, since synthesis of type III collagen is rather weakly expressed in the vessels of the fundus [41]. Separate experimental studies demonstrated (in vitro) the differentiation of perivascular retinal cells into collagen-producing fibroblasts, but their contribution to the formation of a circulating pool of fibroblasts so far needs to be clarified [42].

Apparently, the correlation between the FAZ area and PIIINP level revealed by us may reflect not so much their pathogenic relationship as the simultaneous damage to the retinal microvascular bed and matrix remodeling of other hypertensive target organs — the heart and kidneys, in the tissue and microvasculature of which the expression of this fibrosis biomarker (PIIINP) is considered relatively high. In other words, the established association may serve as an argument in favour of confirming both cardio-ophthalmic and nephro-ophthalmic relationships.

The few available data regarding the dynamics of the choroid thickness in the formation of hypertension and as it progresses indicate mainly decrease of this parameter. So, S. Donati et all (2019) noted that in hypertensive patients (mean age 52.5 ± 3.8 years), the thickness of the choroid was significantly less (251 ± 63 μm) than in healthy individuals (mean age 52.2 ± 4.7 years; SHT 320 ± 61 μm) [11].

According to a study by D. Hua et all (2019) the thickness of the choroid in the center of the foveal region in healthy individuals aged 65 years was 250.7 ± 14.17 μm, which was almost 10 μm higher than that of their peers with hypertension who did not have ophthalmoscopic signs of hypertensive retinal angiopathy [34]. To a certain extent, our own data, based on the assessment of the results of correlation analysis, confirm the role of increasing age (within the middle-age sample) in thinning of the SCT.

In general, the results of our own research and data obtained by other authors confirm the importance of OCTA in relation to the optimization of the search for lesions of target organs at the preclinical stage. The use of this diagnostic method during dynamic monitoring of hypertensive patients in the interest of assessing the state of the microvascular bed and the thickness of the choroid can ultimately help slow down the rate of structural and functional remodeling of the retina.

Conclusions

1. Within the middle-aged sample, patients with uncomplicated essential arterial hypertension are characterized by significantly lower values of the central retinal arterial equivalent and a larger area of the FAZ compared to normotensive individuals.

2. In stage I–II hypertension, the parameters of retinal microcirculation are interrelated with individual cardiovascular risk factors, as well as indicators reflecting the state of other hypertensive target organs — the left parts of the heart and kidneys. The central retinal arterial equivalent correlates with the left atrium volume index, the central retinal venous equivalent correlates with the amplitude of the R wave in the lead aVL of the standard electrocardiogram, the area of the FAZ is associated with 24-h albuminuria and N-terminal propeptide III of procollagen serum concentration.

Conflict of interest

The authors declare no conflict of interest.

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